

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014934 A2

(51) International Patent Classification⁷:

C07J

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:

PCT/EP2003/008505

(22) International Filing Date: 31 July 2003 (31.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2002A001755 2 August 2002 (02.08.2002) IT

(71) Applicant (for all designated States except US): POLI INDUSTRIA CHIMICA SPA [IT/IT]; Via Giuseppe Marcora, 11, I-20121 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GRISENTI, Paride [IT/IT]; Viale Giovanni Da Cermenate, 58, I-20141 Milano (IT). PECORA, Fabio [IT/IT]; Via A. Mantegna 82/A, I-20096 Pioltello (IT). VERZA, Elisa [IT/IT]; Via Oberdan 21, I-20010 Corbetta (IT). LEONI, Massimo [IT/IT]; Via N. A. Porpora 187, I-20131 Milano (IT). BOSSI, Laura [IT/IT]; Via Mezzera 46/2, I-20030 Seveso (IT).

(74) Agent: DRAGOTTI, Gianfranco; Dragotti & Associati Srl, Galleria San Babila 4/C, I-20122 Milano (IT).

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

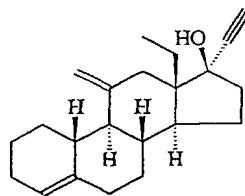
Published:

— without international search report and to be republished upon receipt of that report

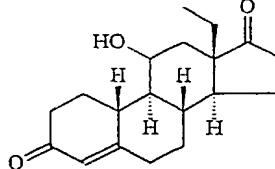
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A2

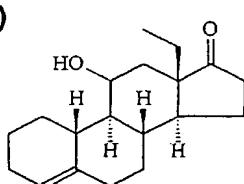
(54) Title: PROCESS AND NEW INTERMEDIATES FOR THE PREPARATION OF STEROIDS WITH A PROGESTOGEN ACTIVITY



(I)



(XIIa)



(XIVa)

WO 2004/014934

(57) Abstract: The present invention relates to a new process of synthesis and to some new intermediates for the preparation of steroids with progestogen activity, more particularly, for the preparation of Desogestrel of formula (I). Said process is characterized by the regioselective reduction of the compound of formula (II) to give the intermediate of formula (III).

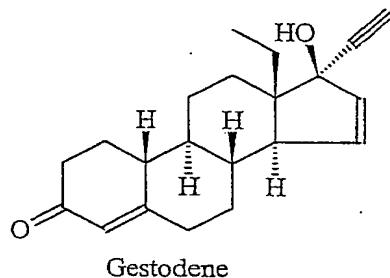
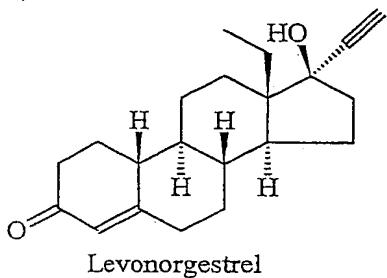
THIS PAGE BLANK (USPTO)

Process and new intermediates for the preparation of steroids with a progestogen activity

The present invention relates to a new process and to new intermediates for preparing compounds with progestogen activity and, more particularly, a process 5 for preparing Desogestrel.

Some synthetic steroidal compounds with progestogen activity such as Desogestrel, Gestodene, Etonogestrel and Levonorgestrel (Fig. 1) have been used in therapy as contraceptives, either alone or associated with estrogens.

10



15

20

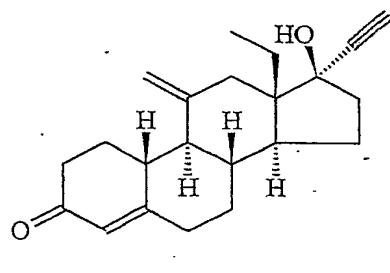
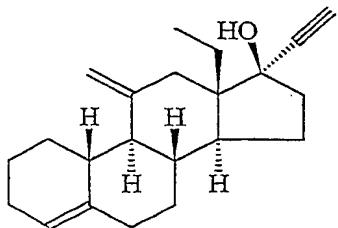


Figure 1. Progestogens of second and third generation

The above mentioned molecules represents the last development of synthetic progestogens, which can minimize the side effects usually associated with the therapeutic use of such compounds. These unwanted side effects, especially related to the therapeutic use of progestogens of the first generation (Figure 2), are mainly represented by an increased risk of cardiovascular diseases and by some hepatic disorders.

30

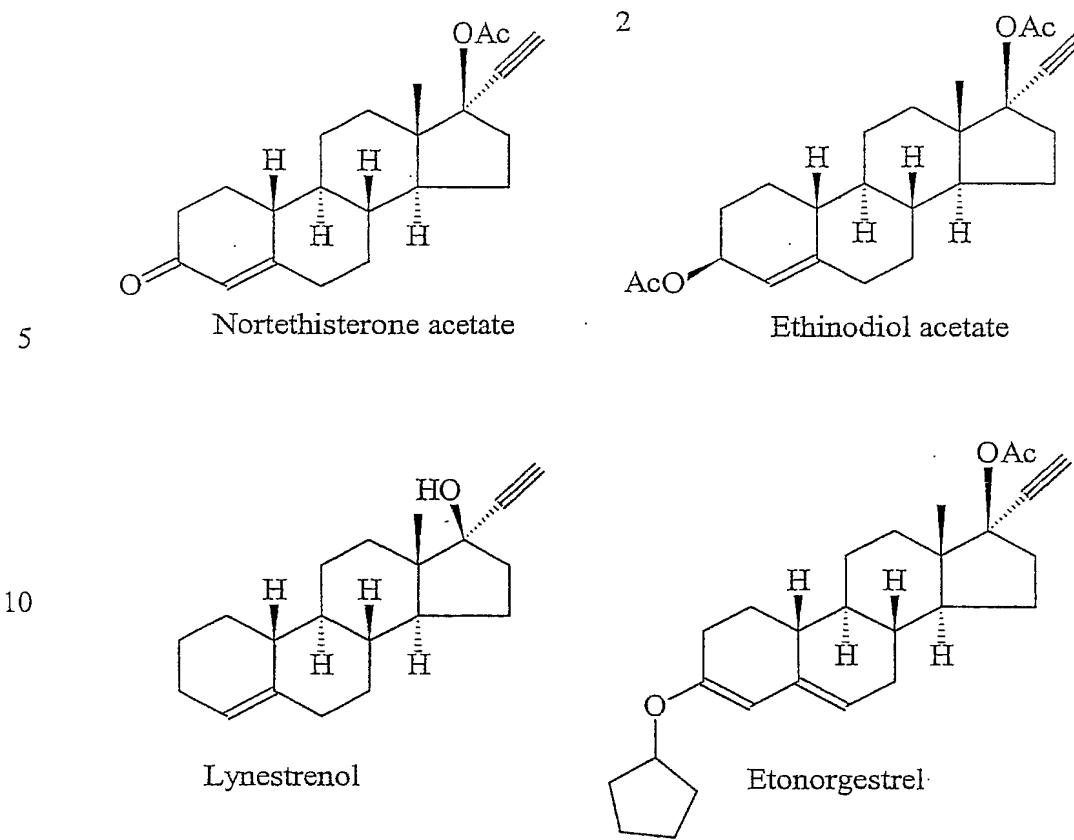


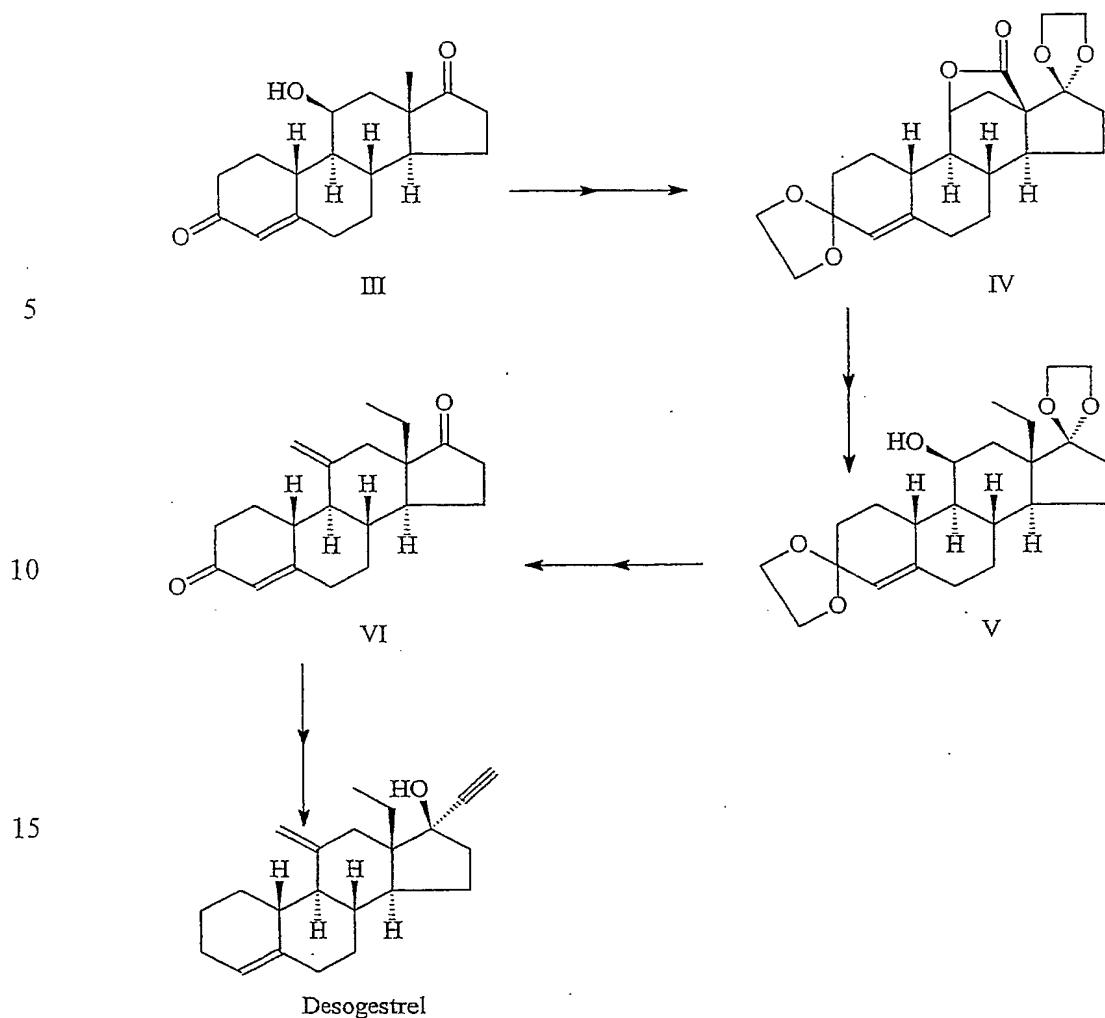
Figure2. Progestogens of first generation

A common structural feature of the second and third generation progestogens is represented by the presence of an ethyl group at the 13 beta position and at the 17 position a beta hydroxyl and alfa ethynyl; Desogestrel represents among these derivatives one of the most used in therapy.

The synthesis of Desogestrel was described, for the first time, in the German patent DE 2.361.120.

They key steps of the synthesis of Desogestrel (scheme 1), described in the above mentioned patent, are the oxidation of the 18 methyl group of the compound of formula III, after protection of the carbonyl groups, to give the lactone of formula IV, the conversion of said lactone into the 13-ethyl steroid of formula V, by a Grignard reaction and Wolff-Kishner reduction, the subsequent oxidation of the hydroxy group at the 11 position into a ketone and the Wittig reaction to furnish the 11-methylene derivative, its deprotection at the 3 and 17 positions to give the dione of formula VI which, by a selective thioacetylation, ethinylation at 17 and reduction of the 3 thioacetal, lead to Desogestrel.

3



20

Scheme 1

This synthetic route is, from a preparative point of view, very troublesome with reference to both the number of steps required and the danger of some reagents used, such as, for example, lead tetraacetate, methylmagnesium bromide and hydrazine.

25 The US patent number US 5,831,104 (Jenapharm GmbH), describes a different synthetic approach for Desogestrel (scheme 2) which starting from the compound of formula VII by reduction of the carbonyl at 3 with cerium chloride/ sodium borohydride, methylation of the so formed hydroxyl and its subsequent reduction leads to the compound of formula VIII which, by oxidation of the hydroxy moieties at 11 and 17 provides the diketones of formula IX.

30

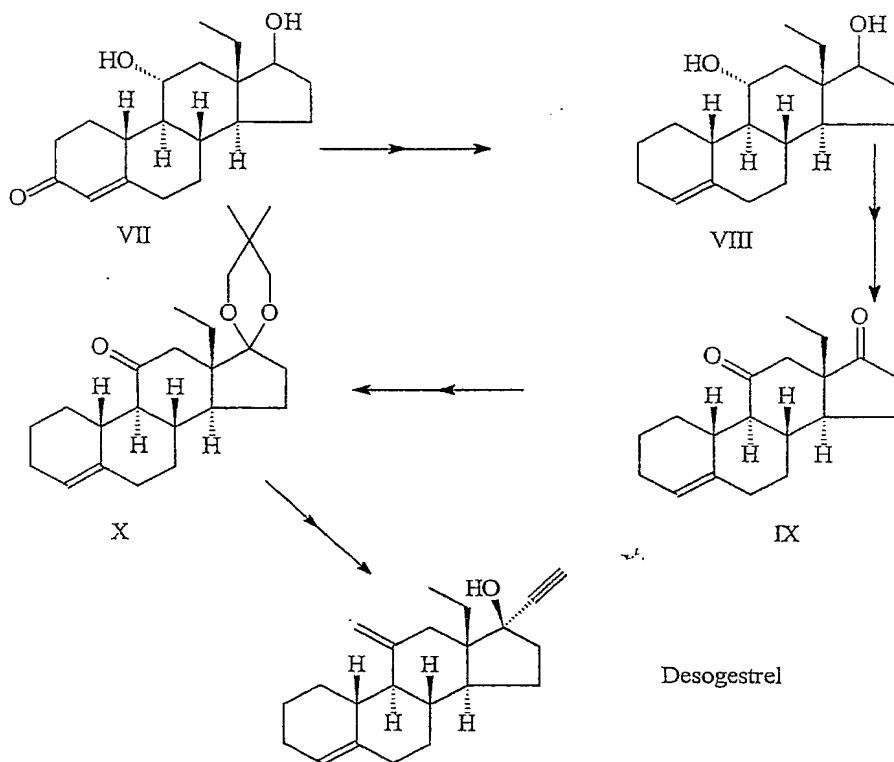
Finally, by selective protection of the ketone at 17 as ketal which affords the compound of formula X, Wittig reaction on the ketone at the 11 position and ethinylation at 17, Desogestrel is obtained.

5

10

15

20



Scheme 2

This second synthetic approach is advantageous in that the starting compound of formula VII, obtainable by total synthesis as described for example in the patent 25 GB 1,128,044, is commercially available.

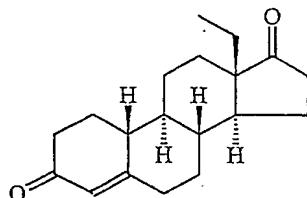
However, the practical realization of what described in the US patent 5,831,104 gives Desogestrel with very low total reaction yields: the ketalization process which should selectively lead to the compound of formula X is, in fact, particularly critical. On this purpose, we have verified that the raw product 30 resulting from ketalization is practically made of a mixture of mono and diketal and that the desired intermediate X must be necessarily purified before going on with the subsequent synthetic steps.

We have now developed a new process for preparing Desogestrel that allows to obtain higher yields through new synthetic intermediates, easily purifyable from reaction by-products.

In addition, the new process allows for using a commercial starting material thus

5 limiting the use of disadvantageous reagents and dangerous reaction conditions.

The compound of formula



XI

10

(13-ethyl-gon-4-en-3,17-dione, RN 21800-83-9), commercially available, is particularly interesting for performing the process object of the present invention in that it has, *inter alia*, the ethyl group already inserted at the 13 position.

15 It may optionally be prepared, as a racemate, as described by H. Smith et al., in Experientia, 19, 394, (1963) and in optically active form (form d) as reported in US 3395080.

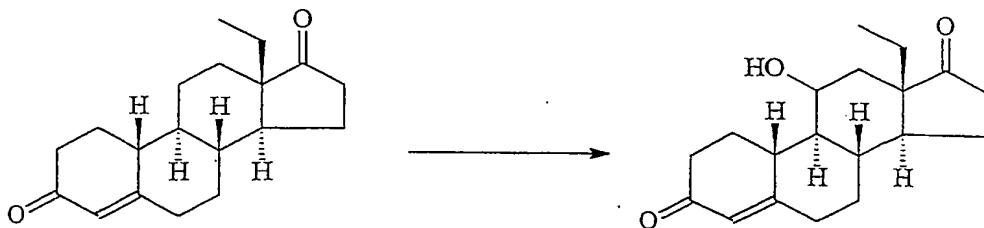
The synthetic steps, needed for providing Desogestrel starting from this substrate, include:

20 · functionalizing the 11 position

· eliminating the carbonyl function which is present at the 3 position.

The introduction of the hydroxy group at the 11 position is performed by microbiological transformation:

25



30

XI

XIIa

Scheme 3

as described in the patent EP0144984.

In particular, after hydroxylation with *Aspergillus ochraceous*, it is possible to isolate, with yields generally varying from 35 to 60%, the corresponding product XIIa, hydroxylated at the 11 position.

5 This microbiological hydroxylation may be performed with a substrate concentration generally between 2 and 6 g/l of biomass, preferably 5 g/l, with a biotransformation time usually of between 20 and 32 hours.

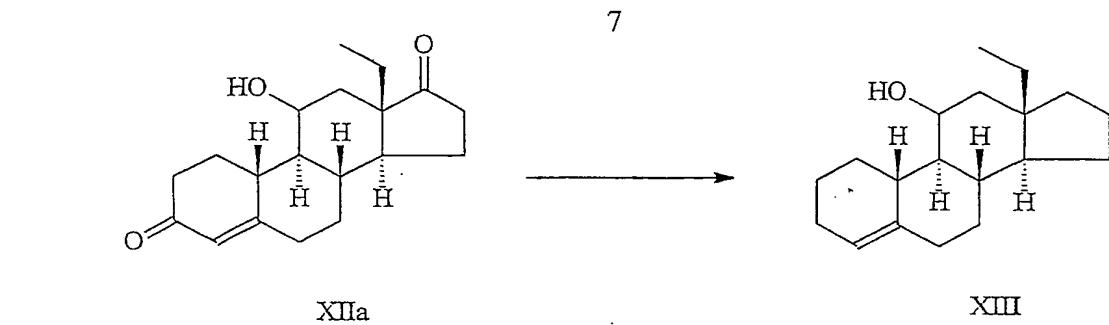
On the so obtained compound XII is then performed the conversion of the 3 keto group into the corresponding CH₂ hydrocarbon function.

10 Several classical reactions of reduction of carbonyl groups are known in the art, such as the Clemmensen reaction, the Wolff-Kishner reaction or the reduction of thioketals that, as known, provide for the use of very toxic (hydrazine, mercury), dangerous reagents (nickel Raney) and extreme experimental conditions (such as, for example, the temperatures required for the reduction of the intermediate 15 hydrazone in the Clemmensen reduction: 150-200°C).

These reactions have been discharged for the above mentioned reasons, in that hardly practicable on an industrial scale and with a great environmental impact because of the toxicity of the produced waste.

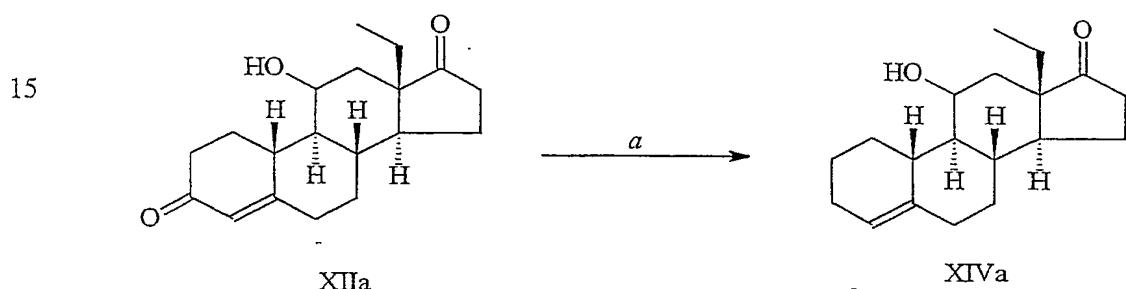
It is known, from the literature, that borohydrides and, in particular, sodium 20 borohydride, are the most handy, from the safety point of view, among the commercially available reducing agents; said reducing agents, which used as such can reduce the carbonyl groups to the corresponding alcohol groups, under determined experimental conditions and by adding particular salts, form mixed hydrides with an increased reducing power, which can reduce functional groups 25 such as amides to amines or ketone compounds to the corresponding hydrocarbon function (US 6,395,901 B1; Gribble et al. *Synthesis*, vol.10, pp763-765, 1978).

Based on what described in the literature, however, it was foreseeable that by applying the above mentioned experimental conditions to the compound of formula XIIa, it should have happened the simultaneously reduction of both the 30 carbonyls at the 3 and 17 positions, to give the compound of formula XIII according to the following scheme:



Scheme 4

Surprisingly, under the herein adopted experimental conditions, a regioselectivity not supported by any literature data was observed, thus allowing to isolate the compound of formula XIVa with high yields. In this reaction (a), in fact, only the ketone group present at the 3 position results transformed into the corresponding hydrocarbon (CH_2), without having the simultaneous reduction of the ketone at 17, as herein disclosed:



Scheme 5

The compound of formula XIV is new and represents a further object of the present invention. It represents a precious intermediate for the preparation of Desogestrel in that it is characterized by the presence of different functional groups at the 11 and 17 positions.

25 This advantageous aspect may be better appreciated if considering the difficulties found during the synthesis of Desogestrel reported in scheme 2, where the simultaneous presence of two ketone groups at the 17 and 11 positions, in the analogous compound of formula IX, requires a not easy chemical manipulation of that substrates in order to obtain a selective protection of only one of the two functional groups.

30

From an experimental point of view such a regioselectivity is never complete and requires a difficult purification procedure of the complex admixture of products.

The above regioselective reduction (a) can be performed by adding the substrate XIIa, dissolved into an organic solvent, to an admixture of alkaline borohydride, a strong organic acid and a C₁-C₃ organic acid, preferably sodium borohydride, trifluoroacetic acid and acetic acid, in a temperature range generally between 0°C 5 and +25°C, preferably at around 20°C, leading to the compound XIVa with yields usually between 57 and 76%.

The alkaline borohydrides which can be advantageously used in this step are represented by sodium and potassium borohydride, preferably by sodium borohydride.

10 The strong organic acid may be any organic acid with a pKa value lower than 2, preferably a derivative of the acetic acid or methansulfonic acid, such as for example trifluoroacetic, difluoroacetic or trifluoromethansulfonic acid, more preferably trifluoroacetic acid.

15 The C₁-C₃ organic acids which can be used in admixture with the trifluoroacetic acid are formic, acetic and propionic acid, preferably acetic acid.

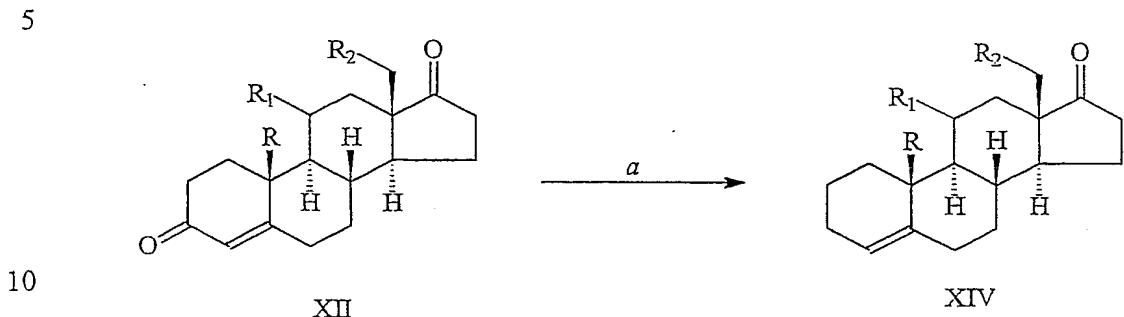
Solvents suitable for dissolving the substrate XIIa in this synthetic step are generally the chlorinated hydrocarbons, simple cyclic or acyclic ethers and polyethers, preferably dichloromethane, tetrahydrofuran or diglyme, more preferably dichloromethane, used alone or in admixture thereof.

20 Such solvents may be used for dissolving the substrate as such or, optionally, in admixture with acetic or trifluoroacetic acid up to a final concentration of acid used at around 2% by volume. In this step the alkaline borohydride is generally used in excess with respect to the substrate XIIa; the ratio between the moles of borohydride and moles of substrate is preferably comprised between 8 and 2, 25 more preferably between 5,5 and 6,5.

The acids are preferably used in excess with respect to the substrate XIIa and in a reciprocal ratio by volume comprised between 2:1 and 1:2, more preferably in a ratio by volume of 1:1.

30 In a preferred embodiment the regioselective reduction is performed with about 6 moles of sodium borohydride per mole of compound of formula XIIa, trifluoroacetic and acetic acid in a ratio by volume of 1:1, in a dichloromethane solution, at a reaction temperature between 0°C and 25°C.

The regioselective reaction of reduction of the carbonyl group at 3 to methylene group, in the presence of a second carbonyl function at 17, above described can be applied to analogous steroidal substrates 3,17 diketo substituted as herein after depicted:



Scheme 5a

in which R_1 and R_2 represent H or CH_3 , and R_1 represents H or OH.

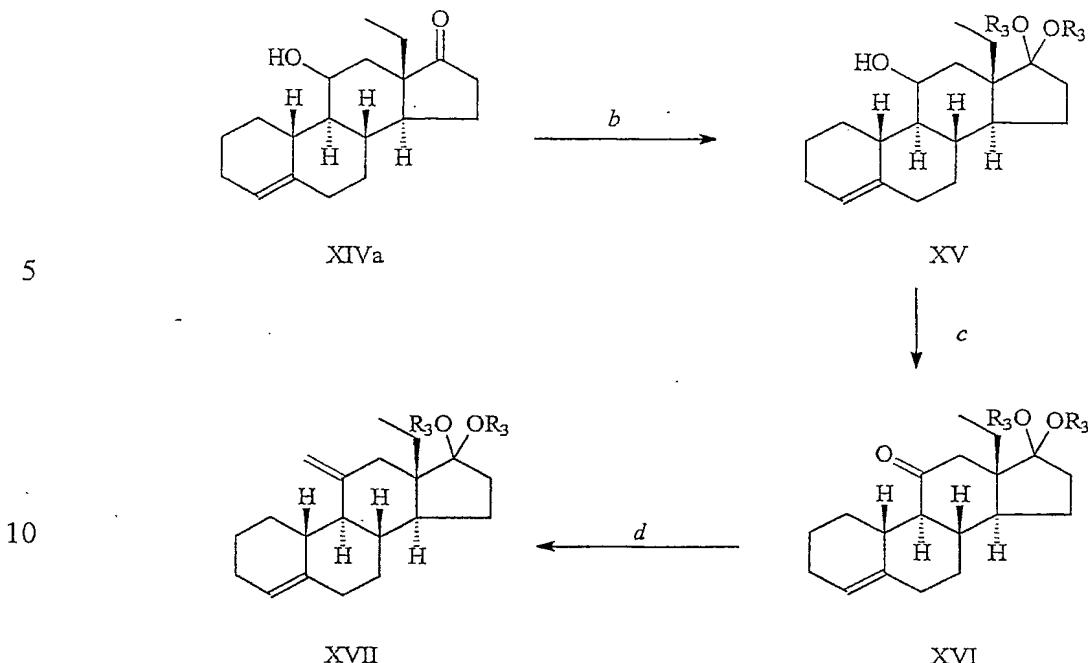
In general the experimental conditions of this reaction of reduction are similar to those already described for the reduction of compound XIIa.

The corresponding products 3-deoxy-17-keto substituted of formula XIV so prepared may found a useful application as intermediates in the manufacturing of therapeutically active steroids such as for example linestrenol.

In a preferred embodiment, the above reaction of reduction is performed on the compound of formula XIIa, in which R=H, R₁=OH and R₂=CH₃, to give the compound of formula XIVa, intermediate useful for the preparation of Desogestrel, in which R, R₁ and R₂ have the same meanings.

The intermediate XIVa is then protected at the 17 position as a ketal (b) and subjected to an oxidative reaction of the hydroxy group at the 11 position (c) and subsequently, at the so formed carbonyl level, to an olefination reaction (d) as herein below represented:

10



Scheme 6

15 in which R₃ represents a C₁-C₅ alkyl or the two R₃ groups together represent a -
(CH₂)_n- chain; wherein n is an integer from 2 to 4, optionally substituted by one or
more methyls.

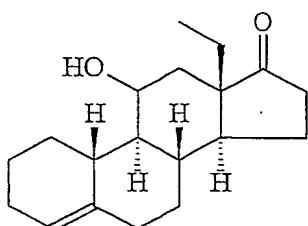
In the sequence above, preferred intermediates are the compounds of formula XV, XVI and XVII protected as cyclic ketals, namely the intermediates in which the two R_3 groups together form a chain $-(CH_2)_n-$ as previously defined, even more preferably the cyclic ketals in which $n=3$, according to the following scheme:

25

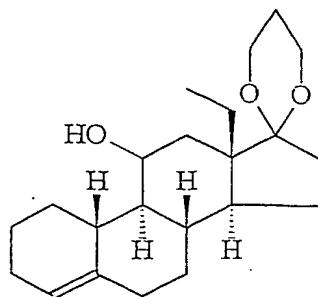
30

11

5

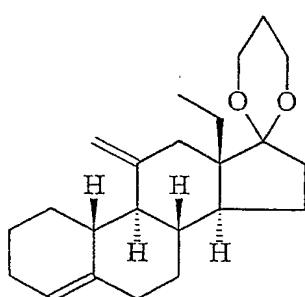


XIVa



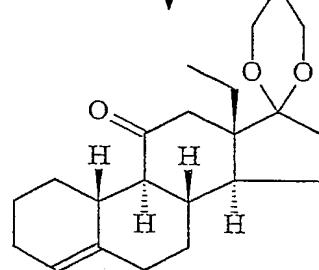
XVa

10



XVIIa

c



XVIa

Scheme 6a

The intermediates, XVIa and XVIIa, in which the two R₃ groups together form a -(CH₂)₃- chain, are new and represent another object of the present invention.

The transformation (b) of the compound of formula XIVa into the ketal of formula XV, is performed under classical conditions of ketalization (see T. Green in *Protective groups in organic synthesis*, third edition, page 297), for example by reaction of the selected alcohol or diol, in amounts generally higher than the stoichiometric ones, in the presence of an orthoester in excess and of an acidic catalyst.

In one of its preferred embodiments such a reaction is performed in a range of temperature between 10 and 50 °C, preferably at about 40°C. in the presence of 4-7 equivalents of 1,3-propandiol, of 2-4 moles of triethylorthoformate per mole of substrate and of p-toluenesulfonic acid in catalytic amount, generally obtaining variable yields from 50 to 80%.

The oxidation reaction (c) of the hydroxy group, present at the 11 position, of the compound XV to give the compound of formula XVI, can be effected by following the classical oxidative methods of alcohols to ketones, for example

according to what described by Carey e Sundberg, in Advanced organic chemistry, third edition, pages 615-624.

Preferably the above oxidation, whose yields generally ranges from 50 to 70 %, is performed by using chromium-based oxidants, such as 10% chromic acid in 9/1 5 pyridine/water (Conforth reagent), pyridinium chlorochromate or 4-dimethylaminopyridinium chlorochromate.

The oxidation reaction is usually performed in an organic solvent selected among dichloromethane, admixtures of dichloromethane and water in the presence of a phase transfer (for ex. tetramethylammonium hydrogensulfate) or in pyridine, 10 preferably in dichloromethane, at a concentration of the substrate XV preferably comprised between 0.05 and 0.2 molar and at a temperature generally comprised between 0°C and 15°C.

The olefination reaction (d) of the compound of formula XVI to give the compound of formula XVII can be performed by a classical Wittig reaction, using 15 methyltriphenyl phosphonium iodide or chloride as phosphonium salt, preferably methyltriphenylphosphonium iodide, in excess, preferably with a molar ratio of about 3:1 with respect to the substrate, and in an aprotic polar solvent such as dimethylsulfoxide, or in an ether such as t-butylmethyl ether or tetrahydrofuran, preferably in dimethylsulfoxide. The base used for preparing the ylide can be a 20 strong organic or inorganic base commonly used in this kind of reactions, for example butyl lithium or sodium hydride, preferably sodium hydride, in ratios generally from 1.1 to 1.5 per mole of phosphonium salt.

The temperature at which the reaction between the ylide and the compound of formula XVI is performed, may be between 40°C and 90°C, preferably at about 25 80°C.

In a particularly preferred embodiment the conversion from XIVa to XVIIa comprises:

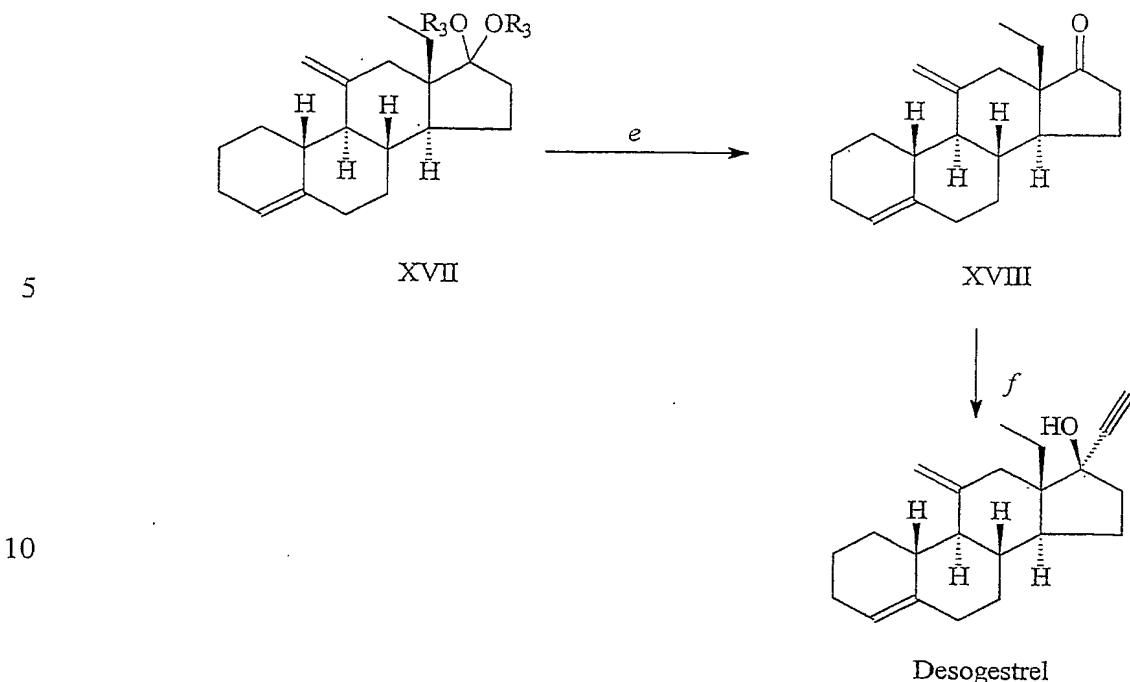
- the protection of the carbonyl group (B) performed in the presence of 4-7 equivalents of 1,3-propandiol, of 2-4 moles of triethylorthoformate per mole of 30 substrate XIVa and of p-toluenesulfonic acid in catalytic amount, at a temperature between 10 and 50°C, preferably at about 40°C.

- the oxidation reaction (c) performed with a chromium based oxidant selected among 10% chromic acid in 9/1 pyridine/water (Conforth reagent), pyridinium chlorochromate and 4-dimethylaminopyridinium chlorochromate in an organic solvent selected among dichloromethane, pyridine and admixtures of dichloromethane and water, in the presence of a phase transfer, at a concentration of substrate XV between 0.05 and 0.2 molar and at a temperature between 0°C and 15°C;
- the olefination reaction (d) by reaction with an excess of methyltriphenylphosphonium iodide or chloride, in an aprotic polar solvent or in an ether, in the presence of a strong base, in ratios between 1.1 and 1.5 moles per mole of phosphonium salt, at a temperature between 40°C and 90°C.

The use the compounds of formula XIIa, XIVa and XV, for the preparation of Desogestrel, is new and inventive and represents a further object of the present invention.

15 The so obtained compound of formula XVII is then deprotected (e) under classical conditions (see for example the already mentioned T. Green in Protective groups in organic synthesis), to give the known intermediate of formula XVIII which, submitted to an ethinylation reaction at 17 (f) as already described in the literature (see for example the already mentioned patent US 5831104), furnishes

20 Desogestrel, according to the following scheme:



Scheme 7

Following the above described synthetic route we have prepared the intermediate of formula XVIII and Desogestrel which show chemical-physical features in compliance with the data reported in the literature (S.Schwarz et al. *Tetrahedron*, vol.50, N°36, pages 10709-10720, 1994).

With the aim to better illustrate the present invention the following examples will now be given.

20 Example 1

Example 1

Preparation of 13-ethyl-11-hydroxy-gon-4-ene-3,17-dione (compound XIIa) from 13-ethyl-gon-4-en-3,17-dione (compound XI)

The starter was prepared in a 5.0 l flask. The medium was prepared starting from 200 ml of a 16.5% glucose solution and 800 ml of an aqueous solution having the following composition:

1. atomized corn steep = 7.00 g/l
2. anhydrous glucose = 33.00 g/l
3. potassium phosphate monobasic = 1.00 g/l
4. potassium phosphate dibasic = 2.00 g/l
- 30 5. sodium nitrate = 2.00 g/l
6. potassium chloride = 0.5 g/l
7. magnesium sulfate heptahydrate = 0.5 g/l

8. iron sulfate heptahydrate = 0.02 g/l

The two solutions were separately sterilized (121°C for 30') and then collected for making the complete medium.

Each flask was inoculated with a slant of *Aspergillus ochraceous* (strain F9- Poli

5 Collection) of about 18 cm² of felt, taken from a slant of Potato Dextrose Agar homogenized in a Potter with 5 ml of physiological solution; 3 flasks were inoculated for a total of 3.0 l of cultural broth. The incubation of the culture was performed on a rotating shaker at 120 rpm at a temperature of 27+/-1°C.

3.0 l of cultural broth were transferred from three flasks into a 5.0 l starter bottle.

10 A first vegetative step was performed in a 200 liters bioreactor and a second growing step in a 1200 liters bioreactor.

The enzymatic activity was induced by addition of 240 ml of a 100 g/l solution of 13-ethyl-gon-4-en-3,17-dione (compound XI) in N,N-dimethylformamide (DMF) to the cultural broth after 8-16 hours from starting the second growing step. After 15 3-6 hours from the end of the addition of the starter solution, a solution of the substrate, prepared from 4.0 kg of 13-ethyl-gon-4-en-3,17-dione (compound XI) in DMF (40.0 liters) was added. The addition was performed continuously for 23-25 hours (33.33 ml/min).

At the end of this period, the fermentation broth was filtered on dicalite (6 kg), 20 washing the obtained cake with ethyl acetate (150 l). The filtered aqueous phase and the organic phase were collected, placed under stirring for 15', and then separated by settling. The aqueous phase was re-extracted with ethyl acetate (2 x 150 l). The organic extracts were collected and concentrated up to a residual volume of 3-4 liters. Such a solution was maintained under stirring at a 25 temperature of 14-16°C for 8 hours; a precipitate was obtained, which was retrieved by filtration and dried under vacuum at a temperature of 60°C for 8 hours. The raw precipitate so obtained was dispersed in dichloromethane (13 kg per kg of dried product) and filtered. The so obtained filtrate was concentrated under vacuum up to a residual volume of 5-7 liters; hexane (26 kg) was slowly 30 added to such a solution, kept under stirring at a temperature of 14-16°C. At the end of the addition the obtained heterogeneous suspension was kept under stirring at a temperature of 14-16°C for 30' then the precipitate was retrieved by filtration.

A humid product was thus obtained, which was dried under vacuum at a temperature of 60°C for 8 hours to give 1.6 Kg of 13-ethy-11-hydroxy-gon-4-en-3,17-dione (compound XIIa).

For analytical purposes, the obtained product was re-crystallized from 5 dichloromethane-hexane to give a sample with the following analytical characteristics:

TLC on silica gel plate using 9/1 dichloromethane/methanol as eluent: r.f. 0.62
 GC (FID) HP-5 30m x 0,25 mm column (0,25 mm film thickness); nitrogen as carrier; injector temperature 300°C, oven temperature: 230°C x 5' then up to 10 280°C (5°C/min), such a temperature was kept for 5': rt of 13' 30".

Mass Spectrum (m/z): 303 (m+1), 302 (molecular ion), 285 (m-17), 274 (m-28), 255 (m-47)

¹H-NMR (500 MHz) in CDCl₃, some of the diagnostic signals can be thus assigned:

<u>δ (ppm)</u>	<u>Attribution</u>	<u>1H-Multiplicity</u>	<u>Integral</u>
0.78	-CH ₂ -CH ₃	t, J=7.5 Hz	3H
1.05-1.25	2CH ₂ ; 9CH; 7CH ₂	complex system	3H
1.30-1.52	14CH; -CH ₂ -CH ₃	complex system	3H
1.52-1.70	15CH ₂ ; 8CH	complex system	2H
1.87-1.95	15CH ₂	m	1H
1.95-2.02	7CH ₂	m	1H
2.09-2.20	16CH ₂	m	1H
2.20-2.52	16CH ₂ ; 10CH; 12CH ₂ ; 2CH ₂ ; 1CH ₂ ; 6CH ₂	complex system	10H
3.82	11CH-O	m	1H
5.84	4=CH	s, broad	1H

Preparation of 13-ethyl-11-hydroxy-gon-4-en-17-one (compound XIVa) from 13-ethyl-11-hydroxy-gon-4-en-3,17-dione (compound XIIa)

A suspension made of sodiumborohydride (152 g) in dichloromethane (0.60 liters) was added to a mixture of trifluoroacetic acid (1.13 liters) in acetic acid (1.13 liters) under stirring at a temperature of 0°C in about 2 hours. At the end of the 5 addition of the suspension of sodiumborohydride, a solution made of 13-ethyl-11-hydroxy-gon-4-en-3,17-dione (201.00 g; 0.66 moles; compound XIIa) in dichloromethane (660 ml) was added to the reaction mixture under stirring at the temperature of 0°C. The reaction mixture was kept under stirring at a temperature 10 of 20°C for 20' then it was cooled at the temperature of 0°C and 4 liters of an aqueous admixture of sodium hydroxide were added (this solution was prepared from 1 liter of water and 3 liters of 30% sodium hydroxide). The reaction was then extracted with dichloromethane (3 x 2.5 liters); the organic extracts dehydrated on sodium sulfate, filtered and concentrated under vacuum to give 15 210.20 g of raw 13-ethyl-11-hydroxy-gon-4-en-17-one (compound XIVa). Such a crude may be further purified by silica gel chromatography (1/5 p/p) by eluting under a gradient of polarity, by using an admixture of toluene and ethyl acetate as mobile phase: by eluting with 9/1 toluene/ethyl acetate 144.67 g (0.50 moles; yields 76%) of pure compound XIVa were obtained, with the following analytical 20 characteristics:

TLC on silica gel plate using 9/1 dichloromethane/methanol as eluent: r.f. 0.77
GC (FID) HP-5 30m x 0,25 mm column (0,25 mm film thickness); nitrogen as carrier; oven temperature: 230°C x 5' then up to 280°C (5°C/min), such a temperature was kept for 5': rt of 13' 30".

25 ¹H-NMR (500 MHz) in CDCl₃, some of diagnostic signals can be so assigned (values in ppm): 1.02 (-CH₂-CH₃, t, J=7.5 Hz, 3H), 2.82 (d, 12 Hz, 1H), 3.80 (11CH-O, m, 1H), 5.40 (4=CH, s, broad)

Example 2 bis

Preparation of 13-ethyl-11-hydroxy-gon-4-en-17-one (compound XIVa) from 13-ethyl-11-hydroxy-gon-4-en-3,17-dione (compound XIIa)

Applying the same procedure described in the example 2, but using difluoroacetic acid and methansulfonic acid, in the same molar ratio, instead of trifluoroacetic acid the following results were obtained:

Acid	Yields of compound XIV (molar %) after chromatography
Difluoroacetic acid	35
Trifluoromethansulfonic acid	38

5

Example 3

Preparation of 13-ethyl-11-hydroxy-17,17-(1,3-propylenedioxy)-gon-4-ene (compound XVa) from 13-ethyl-11-hydroxy-gon-4-en-17-one (compound XIVa)

8.69g (30.17 mmoles) of 13-ethyl-11-hydroxy-gon-4-en-17-one (compound XIVa) were dissolved under stirring at room temperature in 17.4 ml of triethylorthoformate and 12.00 ml of 1,3-propandiol. 518 mg of p-toluenesulfonic acid monohydrate were added to the reaction admixture and the stirring was carried on at the temperature of 40°C for 6 hours. At the end of this period, the reaction mixture was cooled at room temperature and spilled into 43 ml of a saturated solution of sodium bicarbonate, 207 ml of toluene were added and the aqueous phase was separated and re-extracted with toluene (2 x 40 ml). The organic extracts were dehydrated on sodium sulfate, filtered and evaporated under vacuum to give an oily residue of 15.8 g.

For analytical purposes such a crude was further purified by chromatography on alumina (p/p ratio 1/1) by eluting under an increasing gradient of polarity with hexane/ethyl acetate: by eluting with 8/2 hexane/ethyl acetate was obtained a pure sample of the compound XVa with the following analytical characteristics:

TLC on silica gel plate using 8/2 toluene/ethyl acetate as eluent: *rf* 0.57

¹H-NMR (60 MHz) in CDCl₃, some of the diagnostic signals can be so assigned (values in ppm): 0.90 (-CH₂-CH₃, m), 3.45-4.20 (11CH-O e 2-CH₂O, complex system, 5H), 5.50 (4=CH, s, broad)

Example 4

Preparation of 13-ethyl-17,17-(1,3-propylenedioxy)-gon-4-ene-11-one (compound XVIa) from 13-ethyl-11-hydroxy-17,17-(1,3-propylenedioxy)-gon-4-ene (compound XVa)

1.5 g (4.33 mmoles) of 13-ethyl-11-hydroxy-17,17-(1,3-propylenedioxy)-gon-4-ene (compound XVa) were dissolved in dichloromethane (60 ml) under stirring at the temperature of 10°C. 0°C. 4.5 ml of Conforth's reagent (10% rO₃ in 9/1 pyridine/water) were added to the so obtained solution and the stirring of the reaction mixture was continued for 15 hours at room temperature. After this period the reaction was worked-up: isopropyl alcohol was added (3.0 ml) and the stirring of the reaction admixture was continued for other 30'. The reaction admixture was then filtered on Florisil (10 g) washing the cake with 50 ml of dichloromethane. The filtered organic phases were collected and concentrated under vacuum to furnish an oil which is taken up in toluene (10 ml), the so obtained solution was evaporated under vacuum up to an oily residue and then taken up again with toluene (10 ml) and then re-evaporated to dryness: in such a way 1.04 g (3.03 mmoles) of raw intermediate XVIa were obtained.

For analytical purposes such a crude was further purified by chromatography on alumina (p/p ratio 1/15) eluting under a gradient of increasing polarity with hexane/ethyl acetate: by eluting with 95/5 hexane/ethyl acetate a pure sample of compound XVIa was obtained, some analytical characteristics of which are reported:

TLC on silica gel plates using 8/2 toluene/ethyl acetate as eluent: rf 0.68
¹H-NMR (500 MHz) in CDCl₃, some of the diagnostic signals can be so assigned (values in ppm): 1.02 (-CH₂-CH₃, t, J=7.4 Hz), 2.45 (d, 12CH₂, J=12.1 Hz 1H), 2.66 (d, 12CH₂, J=12.1 Hz, 1H), 3.64-4.02 (2-CH₂O, complex system, 4H), 5.44 (4=CH, s, broad)

Example 4bis

Preparation of 13-ethyl-17,17-(1,3-propylenedioxy)-gon-4-ene-11-one (compound XVIa) from 13-ethyl-11-hydroxy-17,17-(1,3-propylenedioxy)-gon-4-ene (compound XVa)

Similarly to what described in the example 4 the oxidation reaction may be performed by using 4-dimethylaminopyridinium chlorochromate as alternative to

the Conforth's reagent. The reaction performed by adding the reagent to the substrate solution (711 mg of compound XV; 2.06 mmoles) in dichloromethane (10 ml) under stirring at room temperature for 40 hours led, after the usual work-up, to 390 mg (1.13 mmoles) of compound XVIa.

5 The chemical-physical characteristics of the obtained sample were in compliance with those reported for the example 4.

Example 5

Preparation of 13-ethyl-11-methylen-17,17-(1,3-propilendioxy)-gon-4-ene

(compound XVIIa) from 13-ethyl-17,17-(1,3-propylendioxy)-gon-4-ene-11-one

10 (compound XVIa)

4.46g of methyltriphenylphosphonium iodide were added to a suspension made of 0.422 g of sodium hydride (60% oily suspension) in anhydrous dimethylsulfoxide (6.02 ml) under stirring at room temperature. The reaction mixture was kept under stirring at the temperature of 80°C for 90' then a solution of 1.15g (3.34 mmoles) 15 of 13-ethyl-17,17-(1,3-propylendioxy)-gon-4-ene-11-one (compound XVIa) in 1.60 ml of anhydrous toluene was added. the reaction was kept under stirring at the temperature of 80°C under inert atmosphere for 15 hours then it was spilled into water cooled at a temperature of about 2°C. The mixture so obtained was extracted with dichloromethane (3 x 20 ml) and the separated organic phase was 20 washed three times with a saturated solution of sodium chloride, dehydrated on sodium sulfate, filtered and evaporated to give an oily crude of about 3.60g. Such a crude was purified by chromatography on alumina (p/p ratio 1/15) eluting with hexane: by eluting with hexane a pure sample of 0.74g (2.17 mmoles; yields 65%) of compound XVIIa was obtained, some analytical characteristics of which are 25 reported:

TLC on silica gel plate using 8/2 toluene/ethyl acetate as eluent: *rf* 0.85

¹H-NMR (500 MHz) in CDCl₃, some of the diagnostic signals can be so assigned (values in ppm): 0.96 (-CH₂-CH₃, t, *J*=7. Hz, 3H), 2.20 (d, 12CH₂, *J*=12.1 Hz 1H), 2.40 (d, 12CH₂, *J*=12.1 Hz, 1H), 3.64-4.00 (2-CH₂O, complex system, 4H),

30 4.72 (=CH₂, s, 1H), 4.92 (=CH₂, s, 1H), 5.44 (4=CH, s, broad)

Example 6

Preparation of 13-ethyl-11-methylen-gon-4-ene (compound XVIII) from 13-ethyl-11-methylen-17,17-(1,3-propilendioxy)-gon-4-ene (compound XVIIa)

1.3 g (3.79 mmoles) of 13-ethyl-11-methylen-17,17-(1,3-propilendioxy)-gon-4-ene (compound XVIIa) were dissolved in acetone (21 ml) under stirring at room 5 temperature. 250 mg of p-toluensulfonic acid monohydrate were added to the solution so obtained and the stirring at room temperature was continued for 17 hours. After this period a saturated solution of sodium bicarbonate (21 ml) was added to the reaction mixture and the organic solvent was evaporated under 10 vacuum. The so obtained aqueous suspension was extracted with dichloromethane (3 x 30 ml) and the organic extracts dried on sodium sulfate, filtered and evaporated under vacuum to give 0.88 g (3.11 mmoles; yields 82%) of the intermediate 13-ethyl-11-methylen-gon-4-ene (compound XVIII).

For analytical purposes such compound can be purified by crystallization from ethanol to give a product with the following analytical characteristics:

15 TLC on silica gel plate using 8/2 toluene/ethyl acetate as eluent: *rf* 0.72

¹H-NMR (500 MHz) in CDCl₃, some of the diagnostic signals can be so assigned (values in ppm): 0.75 (-CH₂-CH₃, *t*, *J*=7.5 Hz), 2.58 (12CH₂, 12,3Hz, 1H), 4.80 (=CH₂, *s*, 1H), 4.90 (=CH₂, *s*, 1H), 5.50 (4=CH, *s*, broad).

m.p.= 99-101°C

20 Example 7

Preparation of Desogestrel from 13-ethyl-11-methylen-gon-4-ene (compound XVIII)

100 g (0.35 moles) of 13-ethyl-11-methylen-gon-4-ene (compound XVIII) were dissolved in anhydrous dimethylsulfoxide (3 liters) under stirring at room 25 temperature. 430 g of lithium acetylide complexed with ethylenediamine were added to the so obtained solution and the stirring at room temperature was carried on for 21 hours. After this period the reaction was spilled in water cooled at a temperature of 2°C (3 liters) then a 10% aqueous solution of acetic acid was added (7 liters) and the aqueous phase was extracted with dichloromethane (3 x 2 30 liters). The organic extracts were subsequently washed with a saturated solution of sodium bicarbonate (2 liters) and then with a saturated solution of sodium

chloride. The organic phase was then dehydrated on sodium sulfate, filtered and evaporated to dryness to give 96.24g (0.31 moles; yields 89%) of Desogestrel. The product thus obtained can be further purified by crystallization from hexane and then from acetone/water to give a sample with the following chemical-
5 physical characteristics:

[α]_D=+57 (c=0.01 chloroform)

DSC melting endotherm at 111.39°C (rate of heating 5°C/min)

IR (2% KBr) values in cm⁻¹:

3541.45 (O-H stretching)

10 3284.98 (stretching acetylenic C-H)

3090.14 (weak)

2103.48 (weak, C=C stretching)

1639.94 (medium)

1033.39 and 1042.91 (C-O stretching)

15 909.80 and 897.87 (out of plane, =CH2)

Calculated elementary analysis for C₂₂H₃₀O:

theoretical values: C. 85.11; H. 9.74; O. 5.15;

Found values: C. 85.09; H. 9.72

Mass Spectrum (m/z): 311 (m+1), 310 (molecular ion), 294 (m-16), 282 (m-28),

20 264 (m-46)

¹H-NMR (500 MHz) in CDCl₃

<u>δ (ppm)</u>	<u>Attribution</u>	<u>1H-Multiplicity</u>	<u>Integral</u>
8.70-9.70	7CH ₂	m	1H
1.10	-CH ₂ -CH ₃	t J=7.5 Hz	3H
1.70-1.17	1CH ₂	m	1H
1.26-1.42	9CH; 8CH; 15CH ₂	complex system	4H
1.42	-CH ₂ -CH ₃	q J=7.5Hz,	2H
1.55-1.68	7CH ₂ ; 3CH ₂	complex system	3H
1.72-1.80	14CH	m	1H
1.86-1.98	6CH ₂ ; 2CH ₂	m	3H
2.03-2.15	16CH ₂	m	1H
2.16-2.28	10CH; 1CH ₂ ; 6CH ₂ ; 12CH ₂	complex system	4H
2.58	acetylenic CH	s	1H
2.60	12CH	d J=12.4 Hz	1H
4.76	=CH ₂	s	1H
4.96	=CH ₂	s	1H
5.44	4=CH	s, broad	1H

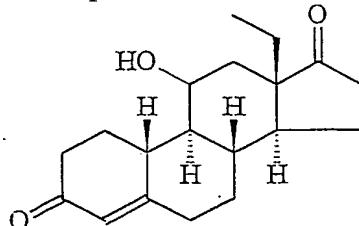
¹³C-NMR (125.721 MHz) in CDCl₃

<u>$\delta^{13}\text{C}$(ppm)</u>	<u>Attribution</u>	<u>Frequency</u>	<u>Intensity</u>
148.2076	C-11	18638.454	2.267
140.5835	C-5	17679.647	1.945
122.0206	C-4	15345.200	4.642
109.1980	=CH ₂	13732.644	4.6228
88.5589	-C≡CH	11137.081	2.004
81.8279	C-17	10290.601	1.472
74.7362	-C≡CH	9398.758	4.300
55.3591	C-9	6961.911	5.936
53.1152	C-14	6679.716	6.090
51.1012	C-13	6426.440	1.755
43.2883	C-8	5443.900	5.708
41.3149	C-12	5195.717	5.533
40.4963	C-16	5092.782	5.747
37.2807	C-10	4688.386	5.766
36.2203	C-6	4555.036	5.794
32.4107	C-7	4075.935	5.276
29.7885	C-1	3746.178	5.791
26.3767	C-2	3317.109	5.802
22.6318	C-3	2846.148	5.944
22.5902	C-15	2840.920	4.822
20.5044	CH ₂ -CH ₃	2578.610	5.001
9.8278	CH ₂ -CH ₃	1235.935	3.717

CLAIMS

1) A process for the preparation of Desogestrel, which comprises the regioselective reduction of the compound of formula

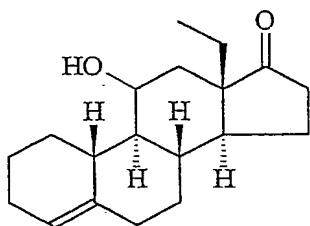
5



XIIa

to give the compound of formula

10



XIVa

15 2) A process according to claim 1 in which said reduction is performed in the presence of an alkaline borohydride, a strong organic acid and a C₁-C₃ organic acid.

20 3) A process according to claim 2 in which said borohydride is sodium borohydride, said strong organic acid is trifluoroacetic acid and said C₁-C₃ organic acid is acetic acid.

25 4) A process according to claim 2 in which said reduction is performed in an organic solvent selected among dichloromethane, tetrahydrofuran or diglyme, preferably dichloromethane.

5) A process according to claim 2 in which the ratio between the moles of borohydride and the moles of compound XIIa is between 8 and 2, preferably between 5.5 and 6.5.

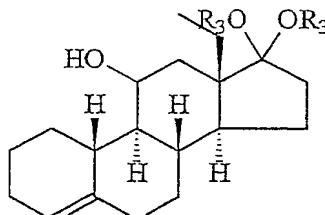
6) A process according to claim 3 in which trifluoroacetic acid and acetic acid are used in a ratio by volume from 2:1 to 1:2, preferably in a ratio by volume of 1:1.

7) A process according to claim 1 in which said reduction is performed with about 30 6 moles of sodium borohydride per mole of compound XIIa, trifluoroacetic acid and acetic acid in a ratio by volume of 1:1, in dichloromethane and at a temperature of reaction between 0°C and 25°C.

8) A process according to claim 1 which further comprises:

(b) the protection of the carbonyl group of the compound of formula XIVa to give the protected compound of formula

5



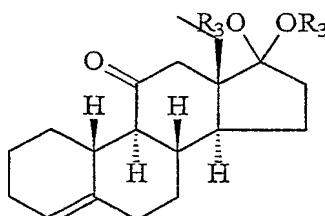
XV

in which

10 R₃ represents a C₁-C₅ alkyl group or the R₃ groups together represent a -(CH₂)_n- chain wherein n is an integer from 2 to 4, optionally substituted by one or more methyl groups;

(c) the subsequent oxidation reaction of the protected compound of formula XV to give the compound of formula

15

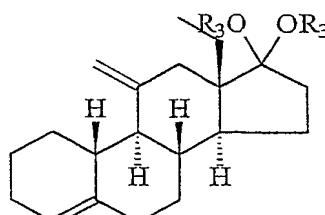


XVI

20 in which R₃ has the above reported meanings;

(d) the subsequent olefination reaction of the compound of formula XVI to give the compound of formula

25



XVII

in which R₃ has the above reported meanings.

9) A process according to claim 8 in which the two R₃ groups together form a -

30 (CH₂)_n- chain wherein n is equal to 3.

10) A process according to claim 8 in which the protection of the carbonyl group

(b) is performed in the presence of 4-7 equivalents of 1,3-propandiol, of 2-4 moles

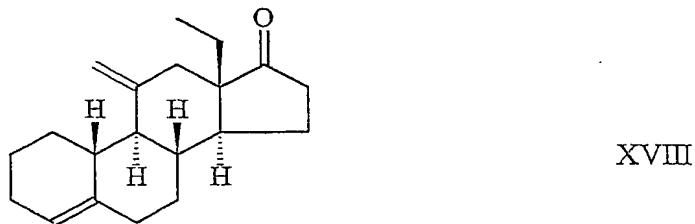
of triethylorthoformate per mole of substrate XIVa and of p-toluenesulfonic acid in a catalytic amount, at a temperature between 10 and 50°C, preferably at about 40°C.

11) A process according to claim 8 in which the oxidation reaction (c) is performed with a chromium based oxidant selected among 10% chromic acid in 9/1 pyridine/water (Conforth's reagent), pyridinium chlorochromate and 4-dimethylaminopiridinium chlorochromate, in an organic solvent selected among dichloromethane or admixtures of dichloromethane and water, in the presence of a phase transfer, or pyridine, at a concentration of substrate XV between 0.05 and 0.2 molar and at a temperature between 0°C and 15°C.

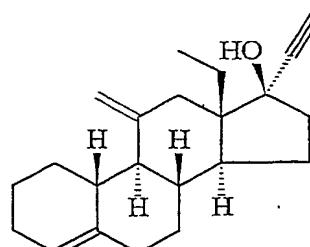
12) A process according to claim 8 in which the olefination reaction (d) is performed by reaction with methyltriphenylphosphonium iodide or chloride, in a polar aprotic solvent or in an ether, in the presence of 1.1-1.5 moles of a strong base per mole of phosphonium salt, at a temperature between 40°C and 90°C.

15) 13) A process according to claim 8 which further comprises:

(e) the deprotection reaction of the compound of formula XVII to give the compound of formula



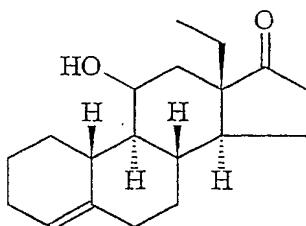
(f) the subsequent ethinylation reaction at the 17 position of the compound of formula XVIII to give Desogestrel of formula



30

14) A process for the preparation of Desogestrel which comprises:

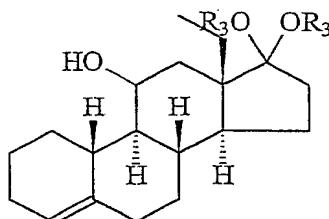
(b) the protection of the carbonyl group of the compound of formula



XIVa

5

to give the protected compound of formula



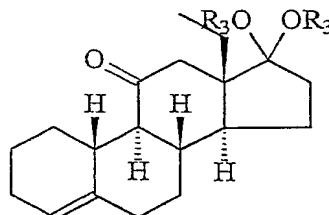
XV

10

in which

R₃ represents a C₁-C₅ alkyl or the two R₃ groups together represent a -(CH₂)_n- chain wherein n is an integer from 2 to 4, optionally substituted by one or more 15 methyl groups;

(c) the subsequent oxidation reaction of the protected compound of formula XV to give the compound of formula

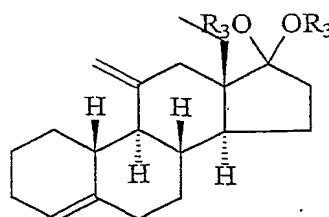


XVI

20

in which R₃ has the above reported meanings;

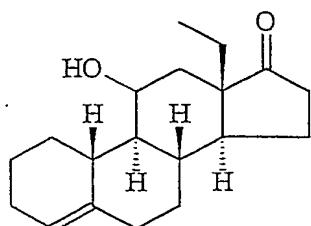
(d) the subsequent olefination reaction of the compound of formula XVI to give 25 the compound of formula



XVII

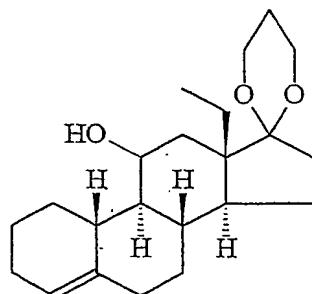
30 in which R₃ has the above reported meanings.

15) The compounds of formula



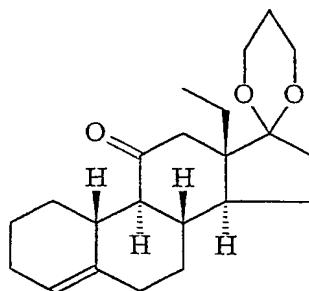
XIVa

5



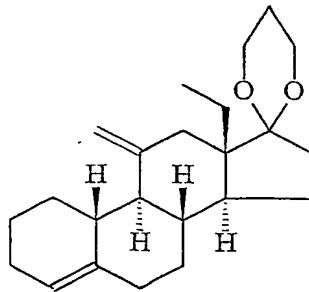
XVa

10



XVIa

15

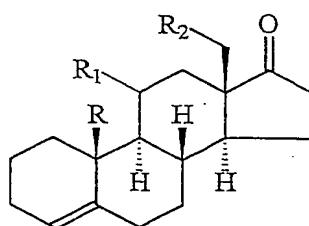


XVIIa

20

16) A process for the preparation of a compound of formula

25

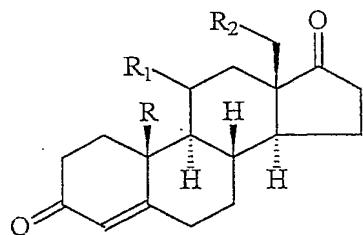


XIV

30 in which

R and R₂ represent H or CH₃, andR₁ represents H or OH,

by regioselective reduction of the compound of formula



XII

in which R, R₁ and R₂ have the meanings reported above.

17) A process according to claim 16 in cui R=H, R₁=OH e R₂=CH₃.

10 18) A process according to claims 16 or 17 in which said reduction is performed according to claims 2 to 7.

19) Use of the compounds of formula XIIa, XIVa and XV as intermediates for the preparation of Desogestrel.

15

20

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014934 A3

(51) International Patent Classification⁷: C07J 11/00,
21/00

(21) International Application Number:
PCT/EP2003/008505

(22) International Filing Date: 31 July 2003 (31.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2002A001755 2 August 2002 (02.08.2002) IT

(71) Applicant (for all designated States except US): POLI INDUSTRIA CHIMICA SPA [IT/IT]; Via Giuseppe Marcora, 11, I-20121 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GRISENTI, Paride

[IT/IT]; Viale Giovanni Da Cermenate, 58, I-20141 Milano (IT). PECORA, Fabio [IT/IT]; Via A. Mantegna 82/A, I-20096 Pioltello (IT). VERZA, Elisa [IT/IT]; Via Oberdan 21, I-20010 Corbetta (IT). LEONI, Massimo [IT/IT]; Via N. A. Porpora 187, I-20131 Milano (IT). BOSSI, Laura [IT/IT]; Via Mezzera 46/2, I-20030 Seveso (IT).

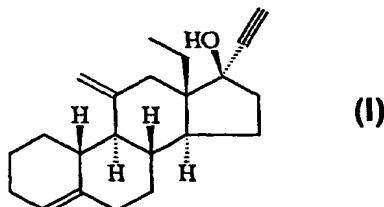
(74) Agent: DRAGOTTI, Gianfranco; Dragotti & Associati Srl, Galleria San Babila 4/C, I-20122 Milano (IT).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

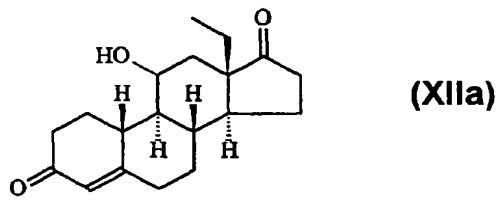
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

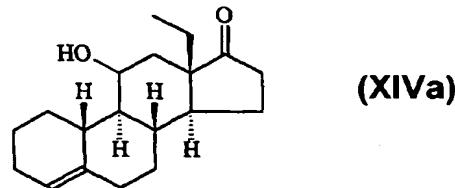
(54) Title: PROCESS AND NEW INTERMEDIATES FOR THE PREPARATION OF STEROIDS WITH A PROGESTOGEN ACTIVITY



(57) Abstract: The present invention relates to a new process of synthesis and to some new intermediates for the preparation of steroids with progestogen activity, more particularly, for the preparation of Desogestrel of formula (I). Said process is characterized by the regioselective reduction of the compound of formula (XIIa) to give the intermediate of formula (XIVa).



(XIIa)



(XIVa)

THIS PAGE BLANK (USPTO)

10/523 058

Rec'd PCT/PTO 02 FEB 2005

WO 2004/014934 A3



Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

21 May 2004

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

THIS PAGE BLANK (USPTO)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08505A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J11/00 C07J21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S. SCHWARZ ET. AL.: "Synthesis of 13-Ethyl-11-methylene-18,19-dinor-17alpha-pregn-4-en-20-yn-17-ol (Desogestrel) and its Main Metabolite 3-Oxo-Desogestrel." TETRAHEDRON, vol. 50, no. 36, 1994, pages 10709-20, XP000611446 pages 10711-13, schemes 4-6	1-19
A	H. GAO ET. AL. : "Synthesis of 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17alpha-pregn-4-en-20-yn-3-one (3-oxo desogestrel)." STEROIDS, vol. 62, 1997, pages 399-402, XP004082728 page 401, scheme 4	1-16

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

12 March 2004

22/03/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Helps, I

THIS PAGE BLANK (USPTO)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08505

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 831 104 A (RING ET. AL.) 3 November 1998 (1998-11-03) cited in the application claims; examples ----	1-16
A	GB 1 128 044 A (HERCHEL SMITH) 25 September 1968 (1968-09-25) cited in the application figure 2; example 17 -----	1-16

THIS PAGE BLANK (USPTO)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08505

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
US 5831104	A 03-11-1998	DE AT DE DK EP ES GR	4330727 A1 182335 T 59408506 D1 643070 T3 0643070 A1 2138641 T3 3031398 T3		16-03-1995 15-08-1999 26-08-1999 28-02-2000 15-03-1995 16-01-2000 31-01-2000
GB 1128044	A 25-09-1968		NONE		

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

BLACK BORDERS

IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

FADED TEXT OR DRAWING

BLURRED OR ILLEGIBLE TEXT OR DRAWING

SKEWED/SLANTED IMAGES

COLOR OR BLACK AND WHITE PHOTOGRAPHS

GRAY SCALE DOCUMENTS

LINES OR MARKS ON ORIGINAL DOCUMENT

REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)